MSN Life Sciences Private Limited

CHLORTHALIDONE

Trail & Validation Status

CHLORTHALIDONE

MSN Life Sciences Private Limited

Total No of Stages: 4
Stage Codes: CRTA1, CRTD1, CRTD2 & CRTD3 (API).
DMF stages: 03 (CRTD1, CRTD2 & CRTD3)
No observations stages : Nil
Issues observed in below stages: CRTA1

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
CRTA1	CRTA100124	Trail	**1) Op.No .64:-** During separation solid formation observed in organic layer. 2) **Op. No . 353:-** Total dry material quantity is 266.20 Kg observed out put is higher than exiting BPR yield range (i.e 207.90 Kg to 254.08 Kg).	1) Due to evaporation loss of MDC (S-807) solvent during quenching & work ups. 2) "Higher Yield Observed due to scale up" of input material.	1) Extra 2 vol of MDC charged in reaction mass for more dilution purpose and moved. 2) Revised the yield range in validation batches i.e 252.87 Kg to 279.51 Kg.

Chlorthalidone

MSN Life Sciences Private Limited

Total No of Stages: 4
Stage Codes: CRTA1, CRTD1, CRTD2 & CRTD3 (API).
DMF stages: 03 (CRTD1, CRTD2 & CRTD3)
No observations stages : Nil
Issues observed in below stages: CRTD1

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
CRTD 1	CRTD1 00124	Trail	**1) Op.No .52:-** As per BPR , Zinc dust filtration to be performed in 2 equal lots, during the Lot-1 reaction mass feeding, based on wet cake thick ness it is observed that filtration can be performed in single lot, hence filtration washing was performed in single lot. **2. Op.No .132**:- As per BPR product filtration to be performed in in 2 equal lots during lot-1 reaction mass feeding , based on wet cake thick ness it is observed that filtration can be performed in single lot. Hence filtration and washing was performed single lot.	1) As the filtration is at hot condition rate of filtration is high & due to high density of zinc dust cake thicknees is less, hence filtration is proposed to single lot . 2) As per physical observation material nature rate of filltration is uniform with respect to increased cake thickness proposed 48'' Centrifugation can accommodate product in single lot.	1) Revised the validation BPR with single Lot filtration. 2) Revised the validation BPR with single Lot filtration and washing.

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Total No of Stages: 4
Stage Codes: CRTA1, CRTD1, CRTD2 & CRTD3 (API).
DMF stages: 03 (CRTD1, CRTD2 & CRTD3)
No observations stages : Nil
Issues observed in below stages: CRDT2

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
CRTD2	CRTD2 00124	Trail	1) **Op.No .120:-** As per BPR, Maintain the Reaction mass 4 to 6 hrs. As per Trial protocol 4th, 5th & 6th hour sample shall be submitted to QC with 1 hour interval but 4th hour, 5th hour sample Sulfonyl chloride impurity content (CRTD2(i) content) obtained Results was 6.2% & 5.8% against the Specification Limit NMT 5.0%. 2) **Op.No. 168 & 205**:- As per BPR provision is available for 3 lots filtration and washing quantity also divided as 3 lots but after 1st lot filtration observed that left over reaction mass is sufficient for 2nd lot only hence washing quantity of 3 lots divided in	1) Maintain time was fixed based on kilo lab BPR but reaction was not moved as per desired level after 4th & 5th hour. 2) As per physical observation material nature rate of filltration is uniform with respest to incraased cake thicknees proposed 36'' centrifuge can accommulate product in two lots.	1) Submitted the further two samples with 3 hrs ± 15 min intervals then submit samples for every 1hr interval till TLC complies. 2) Filtered the left over reaction mass in single lot wash the centrifuge with 127.5 lts of potable water instead of 85 lts.

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Total No of Stages: 4
Stage Codes: CRTA1, CRTD1, CRTD2 & CRTD3 (API).
DMF stages: 03 (CRTD1, CRTD2 & CRTD3)
No observations stages : Nil
Issues observed in below stages: CRDT2

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
CRTD2	CRTD2 00224	**Initial V1 (OOS)**	During the analysis of Related Substances by HPLC test parameter for the Product of Chlorthalidone (stage: CRTD2) Intermediate Batch of B. No.: CRTD200224 (A. R. No.: IM24040152) by using the HPLC instrument (ID. No.: QC-016) on 20/04/2024, OOS was observed w.r.t Sum of Sulfonyl Chloride Impurity and ~2.37 RRT Impurity and Total Impurities. The obtained Sum of Sulfonyl Chloride Impurity and ~2.37 RRT Impurity is 3.7% against to the Specification limit NMT 1.0% and the obtained total impurities is 5.9% against to the Specification limit of NMT 5.0%.	Ref. OOS No. 08-OOS24008 due to suflonyl impurity not washed at washing time raised OOS and Investigated and batch was Rejected.	Then, Reprocess taken with additional acetone + water purification done to eliminate the impurities and shall incorporate the in-process control for Related Substances by HPLC test based on R&D recommends and meeting. Removed & Cancelled this OOS batch (CRTD2 00224) from the Validation Consideration. **CRTD200324** consider as **V1** and batch completed successfully with acetone + water purification. (23 hours in-process taken).
	CRTD2 00424	**V2 (Deviation)**	**08-DR-24-006:** During V2 execution with additional acetone + water purification at OP No. at 122, In-Process Sample analysis result of CRTD2 (i) Content by HPLC test (Sulfonic isomer impurity) got **0.30%** as against the limit of **0.20%.** total 57:00 hours maintained the reaction mass as per at OP No. 116 to	Investigation under Progress. **Validation In-consistency**	Due to Non-complies, another acetone + water purification taken and Sulfonic isomer impurity got **0.26%.** Batch wet condition place Hold. Need to take suggestion from

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Total No of Stages: 4
Stage Codes: CRTA1, CRTD1, CRTD2 & CRTD3 (API).
DMF stages: 03 (CRTD1, CRTD2 & CRTD3)
No observations stages : Nil
Issues observed in below stages: CRTD3

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
CRTD3	CRTD3 00124	Trail	1) **Op.No .59**:- As per BPR , S-805 lot-1 (150 Lts) shall be charged into the reaction mass but S-805 not charged at this operation 2) **Op.No .103**:- As per BPR, spin dry the material under nitrogen atmosphere for 1 to 2 hrs but continue the spin dry for extra 00.30 hrs i.e 02.30 hrs. 3) **Op.No .161 & 162**:- As per BPR, charge purified water lot-11 (30 Lts) into the reaction mass for centrifuge washing but 60 lts purified water charged into the reaction instead of 30 lts and wash the centrifuge with 60 lts purified water.	1) In kilo lob experiment batches acetone higher side OVI obsreved and to avoid the higher side OVI , R&D has suggested charge the same quantity ofter pH adjustment and mintenace at Op. No 96 2) After 2 hours spinning dropwise ML's expelling observed in ML's transfer line hence cantinue the spin dry for extra 00:30 hrs 3) As per R&D instruction , extra 30 Lts purified water uesd for cenfrifuge washing to remove any unwanted chlorider in the material.	1) As per R&D advise, S-805 lot-1, 150 Lts Charged after 2 hrs maintenance of the pH adjustment continue of the maintence for one more hour 2). Spin dry the material up to completion of the MLs. 3). Not applicable

Chlorthalidone

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Total No of Stages: 4
Stage Codes: CRTA1, CRTD1 ,CRTD2 & CRTD3 (API).
DMF stages: 03 (CRTD1 ,CRTD2 & CRTD3)
No observations stages : Nil
Issues observed in below stages: CRTD3

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
CRTD 3	CRTD3 00124	Trail	4) **Op.No .129 & 130** :- As per BPR, charge purified water lot -9 (30Lts) the reaction for centrifuge washing ,but 60 Lts purified water charged into the reactor instead of 30 lts and wash the centrifuge with 60 lts. 5) **Op.No .131**:- As per BPR , spin dry the material under nitrogen atmosphere for 1 to 2 hours but continue the spin dry for extra 00:30 hrs i.e. 02:30 hrs.	4) As per R&D instruction , extra 30 Lts purified water uesd for cenfrifuge washing to remove any unwanted chlorider in the material. 5) After 2 hours spinning dropwise ML's expelling observed in ML's transfer line hence cantinue the spin dry for extra 00:30 hrs.	4) Not applicable. 5) Spin dry the material up to completion of the MLs.

VERICIGUAT

Trail & Validation Status

Vericiguat

MSN Life Sciences Private Limited

Total No of Stages: 4
Stage Codes: VRGT1, VRGT2, VRGT3 & VRGT4 (API).
DMF stages: VRGT1, VRGT2, VRGT3 & VRGT4
No observations stages : Nil
Issues observed in below stages: VRGT1

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
VRGT1	VRGT100124	Trail	1) **Op , No 97 :** - Slowly adjust the reaction mass pH 5 to 7 with M-062 solution through addition tub as per BPR M-062 standard quantity is 3Lts and after 3Lts consumption observed pH paper is 8.0. 2) **Op , No 97 :** - M-062 indented quantity is 10 Lts and to get the desired pH consumed M-062 quantity is 8.5 Lts.	**1)** M-062 Lot-2 quantity may not be sufficient to get the desired pH	1) Indented the additional 10 Lts of M-062 quantity and slowly adjust the reaction mass pH intermittently with pH paper after abtain the pH 6 to 7 submit the sample to QC.
	VRGT100224	**V1 (Deviation)**	Vericiguat stage VRGT1 batch No: VRGT100224 is first Validation in I-Block & F-Block driers on 06/03/2024, observed that the obtained yield is 11.80 Kg, against to the standard	Investigation was performed and it is concluded that suck dry operation performed time for third validation batch is 60 min whereas first and second validation batches are 80 min and 76 min respectively, from overall investigation	Based on investigation team recommendation the yield is recommended as 9.99 Kg to 12.21 Kg by applying the ±10% in average yield of validation

Vericiguat

MSN Life Sciences Private Limited

Total No of Stages: 4
Stage Codes: VRGT1, VRGT2, VRGT3 & VRGT4 (API).
DMF stages: VRGT1, VRGT2, VRGT3 & VRGT4
No observations stages : Nil
Issues observed in below stages: VRGT2

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
VRGT2	VRGT200124	Trail	1) **Op , No 51 & 52 :** - After cooling to 30±5 maintenance for 30 to 40 mints thick reaction mass with sticky in nature observed. 2) **Op , No 58 :** - Thick sticky mass observed in reactor walls after charging of 18 Lts of toluene for washing.	1) During temperature raising and 4 to 6 hrs maintenance reaction mass volume may reduse due to evaporation loss of toluene solvent. 2) Existing 200 volumes (18Lts) of toluene is not sufficient for complete washing of material in reactor.	1) As per BPR recommenddion at operation No.23 charged the additional 1.0 volume (9Lts) of toluene in reaction mass to dilute before going to further cooling. 2) Used additional 1 volume (9Lts) of toluene for washing purpose.

Vericiguat

MSN Laboratories Pvt. Ltd., Unit-III

Total No of Stages: 4
Stage Codes: VRGT1, VRGT2, VRGT3 & VRGT4 (API).
DMF stages: VRGT1, VRGT2, VRGT3 & VRGT4
No observations stages : Nil
Issues observed in below stages: VRGT3

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
VRGT3	VRGT300124	Trail	**1) Op , No 61 :** VRGT2 content by HPLC with sample number VRGT3-04(A) is not meeting the specification limit of NMT 1.0% and the results after 2nd, 3rd & 4th hours are 3.2% w/w, 3.3 % w/w, 2.5% w/w respectively. **2) Op , No 182 :** In-process HPLC analysis of wet material with sample number VRGT3-05 after 2nd purification is not meeting the requirement. Triamine impurity result observed is 0.24% against the specification limit of NMT 0.20%. **3) Op , No 320 :-**Final	**1)** Reaction conversion is slow & reagent quantity is not sufficient. **2)** Triamine impurity reduced from 0.35% after first purification to 0.24% after 2nd purification & Single additional purification is not sufficient to wash the Triamine impurity completely in plant scale. **3)** Additional purification operation performed after 2nd purification to reduce the Triamine impurity lead to less yield.	**1)** used additional 0.5 Kg of M-1482 and maintain the reaction mass for extra 2 to 4 hours and send the sample till 2 consecutive samples complies.& During additional maintenance reaction mass HPLC complies for 4th & 7th hour with results 1.0 % w/w & 1.0 % w/w respectively. **2) P**erformed the additional 3rd & 4th purification with similar process to reduce the Triamine impurity to below the specification limit. **3)** Based on trail batch observation, to revise the yield

Vericiguat

MSN Laboratories Pvt. Ltd., Unit-III

Total No of Stages: 4
Stage Codes: VRGT1, VRGT2, VRGT3 & VRGT4 (API).
DMF stages: VRGT1, VRGT2, VRGT3 & VRGT4
No observations stages : Nil
Issues observed in below stages: VRGT4

Stage No.	Batch Number	Activity	Description of the Issue	Compliance Status of the issue	Current Status
VRGT4	VRGT4 00124	Trail	**1) Op , No 34 :** Solid formation not observed in reactor after prescribed hours i.e 5 Hours **2) Op , No 92 :** Material settling observed in reactor (I/SSR/75/01) because o flow turbulence of reaction mass with 50 agitator RPM during crystallization. 3) During milling operation I/MLR/05 material output flow not observed.	1) Rate of solid formation is low in scale up compared to lab scale. 2) As the reactor geometric volume is low (i.e 50 Lts) existing RPM is not sufficient for required turbulence. 3) Milling not due to nature of material	1)Proposed to maintain the reaction mass at same temperature (30±5 °C) still solid formation observed. 2) Equipment already qualified up to 200 RPM ,based on the physical observation proposed to increase the agitator RPM to 90 3) Proposed to stop the milling operation

FINERENONE

Trail & Validation Status

Finerenone

MSN Life Sciences Private Limited

Total No of Stages: 6
Stage Codes: FRNE1, FRNE2, FRNE3, FRNE4, FRNE5 & FRNE6 (API).
DMF stages: 6
No observations stages : FRNE3 & FRNE5
Issues observed in below Stages: FRNE1, FRNE2

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
FRNE1	FRNE100124	Trial	During The Trial batch Execution BPR Op. No.:88 Lot-1 drying only performed.	After unloading the wet material from centrifuge based on wet material Quality and material nature, Drying performed in Single lot.	Based on Trial Observation proposed to perform the Validation in Single lot.
FRNE2	FRNE2 00124	Trial	Any individual unspecified impurity Specification Limit : Not more the **0.50%** obtained result is **0.49%** in complete analysis.	Based on discussion, AIUI impurity spec limit was relaxed to NMT 1.0% from NMT 0.50% in complete analysis. Aswell In manufacturing process AIUI impurity testing introduded as IPC with limit NMT 0.40% Justification received from AR&D (R&D-13/TR240681/00).	Based on Addendum-4 to PDR , revised in-process & intermediate Spec & MOA (AR-IPFERN6B-0006-001 & AR-IMFERN2-0001-004), manufacturing process validated Successfully.
			Yield range: 96.20 Kg to 117.29 Kg **obtained yield:** 94.20 (Lower yield observed)	Yield range was fixed as per pilot plant, same yield was not achieved in scale up batches in plant level.	Based on trial batch, lower yield range was changed as 84.78 to 117.29 kg with (-)10% of the obtained yield. higher side is as such kept. In validation all three batches within the acceptable limit.

Finerenone

MSN Life Sciences Private Limited

Total No of Stages: 6
Stage Codes: FRNE1, FRNE2, FRNE3, FRNE4, FRNE5 & FRNE6 (API).
DMF stages: 6
No observations stages : FRNE3 & FRNE5
Issues observed in below Stages: FRNE1, FRNE2

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
FRNE2	FRNE200124	Trial	After 18 hrs Maintenance Sample : M-3075 content by TLC Not Complies (Above 7.5%) against the specification limit NMT 5.0%w/w.	Based on R&D recommendation additionally Maintain the reaction mass up to 22 hours. Based on outcome of the batch, fixed the maintenance hours 21 hrs 45 Min ± 15 (at reflex 95°C ± 5°C) for validation batches.	1). V1, V2 & V3 batches TLC results not complies at 22 hour and additional 4 hours maintained through Deviation No**. 08-DR-24-11** and complies the results. 2). Commercial Mfg process recommended as 25 hours 45 minutes ± 15 minutes.

Finerenone

MSN Life Sciences Private Limited

Total No of Stages: 6
Stage Codes: FRNE1, FRNE2, FRNE3, FRNE4, FRNE5 & FRNE6 (API).
DMF stages: 6
No observations stages : FRNE3 & FRNE5
Issues observed in below Stages: FRNE4

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
FRNE4	FRNE4 00124	Trial	1) During the operation (Ref Op. No.:232) M-257 Lot-1 addition Vigorous frothing and gas evaporation was observed for Initial approx. 10% solution addition.	Due to M-771 Quenching with water, frothing and gas was Liberated.	Proposed to Incorporate a note point in the BPR, that initial addition of solution approx. 10% of the M-257 solution to be added very slowly in to the reaction mass to prevent vigorous frothing and gas Liberated.
FRNE4	FRNE4 00124	Trial	2) During the distillation operation (Ref. Op. No.:311) the rate of Distillation in the GLR (E/GLR/16) is Slow.	To reduce the time cycle of the Distillation Operation in GL Reactor, proposed to introduced SS Reactor along with GL reactor.	It is proposed to perform the partial distillation approx. 70% volume will be distilled in SS Reactor (E/SSR/18 & E/SSR/23) and transfer the semi distilled reaction mass from SS Reactors (E/SSR/18/E/SSR/23) to GL Reactor (E/GLR/16 for Final distillation.

Finerenone

MSN Life Sciences Private Limited

Total No of Stages: 6
Stage Codes: FRNE1, FRNE2, FRNE3, FRNE4, FRNE5 & FRNE6 (API).
DMF stages: 6
No observations stages : FRNE3 & FRNE5
Issues observed in below Stages: FRNE4

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
FRNE6	FRNE6 00124	Trial	1) During the trial batch Execution Acetic acid content by HPLC results not compiling the desired Specification limit even after 0.5 mm milling also.	It is noticed that material precipitation gummy material followed by the free floating solution during the addition of Aq. Ammonia to reaction mass and maitenance operation.	Based on Technical report No. R&D-13-TR-FERN-290001-000 and Addendum-06 to Process development report, Process slightly modified. Based on that purification process performed and complies the batch results.

SAMIDORPHAN L MALATE
Trail & Validation Status

Samidorphan-L-Malate

MSN Life Sciences Private Limited

Total No of Stages: 4
Stage Codes: SPLM1 , SPLA1, SPLM2 ,SPLM3 & SPLM4 (API).
DMF stages: SPLM1 , SPLM2 ,SPLM3 & SPLM4 (API).
No observations stages : Nil
Issues observed in below SPLM1, SPLA1 & SPLM2

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
SPLM1	SPLM1001 24	Trail	1) **OP No : 55 :** During the pH. Adjustment final pH. is not with in the limit (8.5 to 9.5) with specified BPR input raw material quantities as per the physical observation on PH paper 7.0.	1) Proposed solution quantity is not sufficient in plant scale.	Proposed to indent the additional quantity of M-470 & Portable water & adjust PH with excess quantity. Total excess quantity consumed is 6.62 Kg of M-470 and final PH. is 8.92.
SPLA1	SPLA1001 24	Trial	Purity by HPLC test of Sample Preparation-1 is 85.8915% and Preparation-2 is 85.4020% against the Specification Limit of "Not Less Than 97.0%“.	Sludge contamination with reaction mass is the root cause for Failure in purity by HPLC.	1) Based on OOS (08-OOS24019) Preventive action BPR Shall be revised as per Addendum-1 inclusion of Reprocess and Revised IP Spec & MOAs (AR-IPSMDA1-0002-001).
SPLM2	SPLM2001 24	Trial	1) **OP No : 16 :** Mid. mixing of reaction mass observed with existing 50 RPM.	1) For reaction completion Vigorous mixing is required.	1) Proposed to increase the RPM from 50 to 130 for Vigorous mixing.

Samidorphan-L-Malate

MSN Life Sciences Private Limited

Total No of Stages: 4
Stage Codes: SPLM1 , SPLM2 ,SPLM3 & SPLM4 (API).
DMF stages: SPLM1 , SPLM2 ,SPLM3 & SPLM4 (API).
No observations stages : Nil
Issues observed in below SPLM3 & SPLM4

Stage No.	Batch Number	Activity	Description of the Issue	Reason of Issue	Remarks
SPLM 3	SPLM300 124	Trial	As per operation, charge M-221 in to the reaction mass. As per BPR clear solution should appear but Not observe the clear solution.	Reaction mass becomes heterogeneous after charging M-221 in to the reaction mass observed the chouck during transfer line from I/SSR/30 to I/SSR/18/01.	Reaction mass unloaded to HDPE container & transfer to I/SSR/18/01 without closed transfer line. Also for upcoming validation batches, it is Proposed to dissolve the reagents (SPLM2, M-1151 & M-440) in 10 volumes of Solvent, transfer to I/SSR/18/01 through closed transfer line & prepare M-221 solution separately in HDPE container with 2.0 Vol of solvent and transfer to I/SSR/18/01.
SPLM 4	V1, V2, V3.	In (V1) batch After 9th hrs crude Drying sample Result not within the specification limit, based on deviation No.: 08-DR-24-020 and R&D justification report (Ref. No. R&D-13-TR-SMDP-240003-000), the specification limit was revised from NMT 5.0%w/w to For information due to down stream operation material dissolved in water only, hence changed the limit. V1, V2 & V3 batches quality results are within the specification limit. Yield Results were obtained lower side yield for the all validation batches. Investigated with Ref. 08-DR-24-024 and standard yield range was fixed based on PDR final process data.			

MSN Life Sciences Private Limited

VONOPRAZAN FUMARATE

Trail & Validation Status

Vonoprazan Fumarate

MSN Life Sciences Private Limited

Total No of Stages: 5
Stage Codes: VFNA1 ,VPNA1, VPNA2 ,VPNA3 & VPNA4 (API).
DMF stages: VPNA1, VPNA2 ,VPNA3 & VPNA4
No observations stages : VFNA1 & VPNA4
Issues observed in below stages:VPNA1, VPNA2, VPNA3

Stage No.	Batch Number	Activity	Description of the Issue	Compliance Status of the issue	Current Status
VPNA 1	VPNA 100124	Trail	1) **Op, No. 61 & 62, 161 & 162:-** S-821 Solvent & M-999 raw material standard Quantity is 50 Lt and 5.00 Kg but used Qty is 25Lt and 2.00kg. 2) **Op, No.107:-** Charge M-230 in to the reactor under Nitrogen atmoshere at 30 ℃ ±5 ℃ but during addition temparature was reached to 38.8 C. 3) **Op, No. 37 & 150:-** M-003 indented qty is 12 cylinders but consumed cylinders are 6.	1) As 25 Lt of S-821 and 2.00kg of M-999 is sufficient for bed formation. 2) Due to exothermic nature the temperature was increased. 3) 6 cylinders is sufficient for the reaction completion.	1) Not Applicable 2) Slowly added M-230 in to the reactor under nitrogen atmosphere at 30 C ±5 C. 3) As per BPR operation no. 37 & 150 after sample collection, continue the maintenance under Hydrogen pressure till TLC result obtained. But in the process after sample collection Hydrogen pressure was released and apply the Nitrogen, continue the maintenance under Nitrogen pressure till TLC result obtained.

Vonoprazan Fumarate

MSN Life Sciences Private Limited

Total No of Stages: 5
Stage Codes: VFNA1 ,VPNA1, VPNA2 ,VPNA3 & VPNA4 (API).
DMF stages: VPNA1, VPNA2 ,VPNA3 & VPNA4
No observations stages : VFNA1 & VPNA4
Issues observed in below stages:VPNA1, VPNA2, VPNA3

Stage No.	Batch Number	Activity	Description of the Issue	Compliance Status of the issue	Current Status
VPNA 1	VPNA 100124	Trail	4) Op, No.264:- Expected yield range is 25.05kg to 34.43kg (50.99%to70.10%) but obtained actual yield is 35.50kg (72.27%).	4) Trial batch expected yield has been fixed based on pilot plant executed batch yield data. The trial batch is higher batch size 52.50 kg and minimize the handling loss and operational efficacy yield might be higher than the expected yield range any how obtained yield is with in the theoretical yield 49.12kg for 52.50kg batch size.	4) Yiled range was changed to 34.0 Kg to 41.65 Kg in validation batches.

Vonoprazan Fumarate

Total No of Stages: 5
Stage Codes: VFNA1 ,VPNA1, VPNA2 ,VPNA3 & VPNA4 (API).
DMF stages: VPNA1, VPNA2 ,VPNA3 & VPNA4
No observations stages : VFNA1 & VPNA4
Issues observed in below stages:VPNA1, VPNA2, VPNA3

MSN Life Sciences Private Limited

Stage No.	Batch Number	Activity	Description of the Issue	Compliance Status of the issue	Current Status
VPNA2	VPNA200124	Trail **(OOS)**	During the analysis of Related Substances by HPLC test parameter for the Product of Vonoprazan fumarate (Stage: VPNA2) Intermediate batch of B. No.: VPNA200124 (A. R. No.: IM24040187) by using the HPLC instrument (ID. No.: QC-017) on 27/04/2024, out of specification result was observed with respect to 2-Fluoro Carbaldehyde Impurity and 2-Fluoro Cyano Pyridine Impurity. The obtained result of 2-Fluoro Carbaldehyde Impurity is 0.23% against the Specification limit of 0.20% and the obtained result of 2-Fluoro Cyano Pyridine Impurity is 0.23% against the Specification limit of 0.15%. (Reference Specification No.: AR-IMVPRN4B-0001-000).	(Ref OOS No. 08-OOS24010) Investigation completed and spec&MoA has been revised by relaxing the specification limits	Recompiled the results with revised speciation and MOA with reference No. AR-IMVPRN4B-0001-001 Based on compiled data, the batch results are within the specified limit.

Vonoprazan Fumarate

Total No of Stages: 5
Stage Codes: VFNA1 ,VPNA1, VPNA2 ,VPNA3 & VPNA4 (API).
DMF stages: VPNA1, VPNA2 ,VPNA3 & VPNA4
No observations stages : VFNA1 & VPNA4
Issues observed in below stages:VPNA1, VPNA2, VPNA3

MSN Life Sciences Private Limited

Stage No.	Batch Number	Activity	Description of the Issue	Compliance Status of the issue	Current Status
VPNA2	VPNA200124	Trail	During the Trial batch execution Extra one hour maintained in drying operation for Second consecutive sample conformation purpose.	Compare to Kilo lab per tray quantity in Drier in plant scale is high, hence the drying time is increased.	Proposed to perform drying for 5 hours±15 min in Validation batches.
VPNA3	VPNA300124	Trial	Water content of reaction mass not complies after co-distillation with S-811 Lot-4	Based on available vacuum and utility temperature at plant scale two times co-distillation is not sufficient, hence proposed for additional co-distillation.	Proposed to perform additional co distillation with S-811 Lot-5 at operation number 119 to 126 to meet the desired water content.
			24.50 kg output with 44.40% yield observed in trial batch against the BPR yield range of 33.28 Kg to 49.93 Kg (60.32% to 90.48%).	Compare to lab scale lower yield observed in plant scale because of difference in mixing, distillation and filtration operations during execution of trial batch	Based on trial batch obtained yield and R&D recommendations, the yield range was revised to 24.50 Kg. to 49.93 Kg from 33.28 Kg. to 49.93 Kg
			Slightly low wet weight obtained.	It is recommended to add solvent quantity based on wet weight instead of batch input quantity.	To avoid further yield loss in purification step.(R&D technical report No.R&D-13/TR240521/00

MSN Life Sciences Private Limited

ATOGEPANT
Trail & Validation Status

ATOGEPANT

MSN Life Sciences Private Limited

Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 , AOGT3 & AOGT4 (API).
DMF stages: AOGT1 , AOGT2 , AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

Stage No.	B. No	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Proposal for Trial-2 batch	Remarks
AOGT1	AOGT100124	Trial	115	During distillation solid precipitation observed.	Unload residue in HDPE Container and weigh (46.60 kg) and dissolved in 20 lit DMSO, The precipitated solid material unload separately and weighing (3.91 kg) and kept aside.	This solid material precipitated is Sodium Sulfate which was used for dehydration in the previous operation. This was carry forward from the filtration process and this was no impact on the process.	It was proceed as such and perform the filtration operation with care in the Trial-2 batch.	Observation closed at plant end.

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 , AOGT3 & AOGT4 (API).
DMF stages: AOGT1 , AOGT2 , AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2, AOGT3 & AOGT4

Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Proposal for Trial-2 batch	Remarks
AOGT 1	AOGT 100124	Trial	257	TLC complies after 20 hrs Maintenance (AOGT1(iii) Content limit is NMT-5.0%) in QC, in AR&D observed approx. 20% above.	Based on R&D Use tests continued for the second lot Enzyme.	There is a discrepancy in the results from QC to AR&D and based on the plant use test, it was decided to proceed further by adding excess equivalents of Isopropyl amine and quantities of Enzyme to complete the reaction. But the TLC was compiled close to the specification limit.	proceed as such and the TLC analysis done in the presence of the AR&D personnel to understand the variation. Based on the outcome of the Trial-2 batch decision for validation batches will be taken.	Observation closed at plant end.
			265	TLC not complies after 10 hr maintenance Sample in AR&D	Charge M-4149 Lot-3			
			275	TLC not complies after 10 hr maintenance Sample in AR&D	Charge M-5093 lot-2 (Enzyme) and M-4149 Lot-4 Solution			

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 ,AOGT3 & AOGT4 (API).
DMF stages: AOGT1, AOGT2 ,AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Proposal for Trial-2 batch
AOGT 1	AOGT1 00124	Trial	301	Enzyme (unwanted salt) passes through Centrifuge filter ML's while filtration	Reaction mass filter through hyflo bed , till salt observed in filter ML, Collect total filtrate in Reactor and decent clear reaction mass in another reactor	Enzyme (unwanted salt observed in filtrate during centrifuge	Hyflow bed preparation is included in the BPR based on Trial-1 observations.
AOGT 1	AOGT1 00224	Trial	95	Filtration activity became slow due to formation of Aglumination of M-670 material.	As per R&D recommendation, it is proposed to increase the reaction mass temperature to 25±5°C and slowly charge M-670 using scoop.	At 10±5°C temperature filtration activity became slow due to formation of Agglutination of M-670 material.	Before charging M-670 material, temperature raising operation included in validation BPR.

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 ,AOGT3 & AOGT4 (API).
DMF stages: AOGT1, AOGT2 ,AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Remarks
AOGT 2	AOGT2 00124	Trial	88 to 144	During M-799 washing of Organic layer it was observed that the reactor volume was reaching to over flow.	current batch workup was performed in the I/SSR/13 as M-799 is the week acid, but it proposed to include an additional GLR for the workup activity for Validation batches	...	Additional equipment to be included in Validation batches
AOGT 3	AOGT3 00124	Trial	28 34	As per BPR instruction Qty of M-799 to be charged as **0.087 kg** in 35 Lts of Potable water but we have charged only **0.035 kg** in 35 Lts of water	BPR revised with the proposed Qty of M-799 for the Validation batches.	As per the justification report dated 07-08-2024 received from R&D Ref. Technical Report no.:R&D-13/TR240724/00. [(M-799) citric acid 0.25% solution washings used for N-Methyl Impurity controlling Purpose, but approx. 15% of yield loss observed	Included in validation BPR

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 ,AOGT3 & AOGT4 (API).
DMF stages: AOGT1, AOGT2 ,AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

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Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Remarks
AOGT 3	AOGT3 00124	Trial	125 (a)	As per BPR instruction 56 Lts of S-810 to be charged in to the residue at 30°±5°C, but 28 Lts, charged instead of 56 Lts of S-810 into the residue mass.	Based on errata, proposed BPR provided by the R&D 28 Lts of S-810 is used for the dissolution of the residue and same is proposed for The Validation batches	Typo error observed in the proposed BPR (8.0 Volumes instead of 4.0 volumes)	included in validation BPR
AOGT 3	AOGT3 00124	Trial	129	As per BPR instruction, 28 Lts of S-810 to be charger into the reactor for reaction purpose at 35°±5°C but charged 56 Lts instead of 28 Lts of S-810 into the Reaction mass	Based on Errata, proposed BPR provided by the R&D 56 Lts of S-810 is used for the reaction and same is proposed for the Validation batches.	Typo error observed in the proposed BPR (4.0 volumes instead of 8.0 Volumes)	included in validation BPR
AOGT 3	AOGT3 00124	Trial	147	Approx. 10 mL of Additional sample collected after batch maintained for 3 to 4 hrs at	Samples will be included in the protocol for validation	For Additional Study purpose	Included in Validation protocol

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 ,AOGT3 & AOGT4 (API).
DMF stages: AOGT1, AOGT2 ,AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Remarks
AOGT 3	AOGT30 0124	Trial	164	Approx. 10 mL Organic Layer and approx. 10mL Lot-02 Layer collected after layer separation as additional sample and stored at ambient condition	Samples will be included in the protocol for validation batches	For Additional Study purpose	Included in Validation protocol
AOGT 3	AOGT30 0124	Trial	171 180 188 196 204	~10 mL of Organic Layer and 10 mL of Aq.Layer separation as additional sample and will be stored at ambient condition	Samples will be included in the protocol for validation batches	For Additional Study purpose	Included in Validation protocol
AOGT 3	AOGT30 0124	Trial	208	10 mL of distilled residue sample collected after distillation as additional sample and will be stored at ambient	Samples will be included in the protocol for validation batches	For Additional Study purpose	Included in Validation protocol

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 ,AOGT3 & AOGT4 (API).
DMF stages: AOGT1, AOGT2 ,AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Remarks
AOGT 3	AOGT30 0124	Trial	218 223 248	Approx. 5.0gm of wet material & approx. 50mL of centrifuge filtrate MLs sample collected as additional sample and it will be stored at ambient condition.	Samples will be included in the protocol for validation batches.	For Additional Study purpose.	Include in Validation protocol.
AOGT 3	AOGT30 0124	Trial	271 285	Approx. 5.0gm of Dry material sample collected, after 2 hrs air drying as additional sample and will be stored at ambient condition.	Samples will be included in the protocol for validation batches.	For Additional Study purpose.	Include in Validation protocol.
AOGT 3	AOGT30 0124	Trial	289	Out of range/Higher yield of 5.50 Kg observed against the standard yield range 3.57 Kg to 4.34 Kg.	Yield range shall be revised for Validation batches.	NA	Based on trial batch obtained yield, recommend to increase the higher side with +10% of the Trial batch obtained yield for Validation.

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 ,AOGT3 & AOGT4 (API).
DMF stages: AOGT1, AOGT2 ,AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Remarks
AOGT4	AOGT400124	Trial	23	At the end of distillation operation a thick residue was formed and volume was less than the stirrable volume of the reactor so Nitrogen expelling was performed at the end of distillation to remove methanol traces from isolated material.	Proposed to install additional Teflon blades for upcoming validation batches so, that the reactor meets the minimum stirring requirments of this product.	additional Teflon blades to be installed for upcoming validation batches.	NA

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 ,AOGT3 & AOGT4 (API).
DMF stages: AOGT1, AOGT2 ,AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Remarks
AOGT 1	AOGT100424 (V2)	Validation (Yield Deviation)	NA	The Second validation batch of Atogepant product of stage AOGT1 of Batch No. AOGT100424 was manufactured Input of Batch Size is 50.00 Kg of M-2521 in I-Block & E- Block Drying Area on 28/08/2024, observed that the obtained yield is 18.00 kg against the expected yield range is 12.00 Kg. to 17.50 Kg. The Theoretical Yield is 72.45 Kg . **Ref Deviation No:08-DR-24-015**	1. Shall be revise the BPR (Reference BPR format No.: F-AOGT1-01/02) by incorporate a note point as "Check the clarity of the layers while separation, if observed any emulsion record the details in remarks column" in all the operations where work-up's/extractions are involved. 2. After completion of two or more commercial batches with revised BPR, the appropriate preventive action shall be taken.	From the overall investigation, the probable cause for the occurred deviation with respect to yield parameter (i.e., higher yield) is due to operational efficiency at plant scale, moreover there is no measuring mechanism for the obtained waste streams in the Process and the quantities may vary from batch to batch which might lead to yield variations & not identified the confirmed root cause.	Revised the BPR by covering the validation batches outcome yield and fixed.

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 ,AOGT3 & AOGT4 (API).
DMF stages: AOGT1, AOGT2 ,AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Remarks
AOGT2	AOGT200224 (V1)	Validation (Procedure Deviation)	NA	Atogepant Product of Intermediate Stage of Stage Code: AOGT2 (First Validation Batch) of B. No.: AOGT200224 was executed as per BPR (Reference BPR Format No.: F-AOGT2-01/01) in I-Block and D-Block, E-Block and F-Block Drier Area whereas the additional In-Process Samples monitoring during the process was not followed as proposed in the Validation Protocol (Reference Protocol Number: 08-AOGT2-PVP-2024-0001-000). However, the BPR Samples has been monitored as per BPR Operations, found meeting the Specification Limits. **Ref Deviation No:08-DR-24-015**	An awareness Training was imparted to concerned personnel on Validation Protocols and on SOP of Filling of Batch Production Record, Batch Cleaning Record and Area Cleaning record (Reference SOP No.: CPD-0009) and Good Documentation Practices SOP (Reference SOP No.: CQA-0013).	The Root cause for the occurred deviation is due to the operating personnel who were involved in activity inadvertently not followed the Protocol Procedure.	NA

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Total No of Stages: 5
Stage Codes: AOGT1 ,ATGN1, AOGT2 ,AOGT3 & AOGT4 (API).
DMF stages: AOGT1, AOGT2 ,AOGT3 & AOGT4
No observations stages : ATGN1
Issues observed in below stages: AOGT1, AOGT2 ,AOGT3 & AOGT4

Stage No.	B.No.	Activity	Op. No.	Observation	Action Proposed	Justification / Reason	Remarks
AOGT1	AOGT100824 (V1)	Scale-up Validation Higher Yield Deviation)	NA	The First Scale up Validation batch of Atogepant Product of Stage AOGT1 of B. No.: AOGT100824 was manufactured with input batch size of 100.00 Kg of M-2521 in I-Block and A-Block intermediate area and A-Block / B-Block Drying area on 09/11/2024, observed that the obtained yield is 43.10 Kg against the expected yield range is 24.00 Kg to 30.00 Kg. The theoretical Yield is 144.91 Kg.	NA	higher yield obtained due to consume the additional quantity of the raw material of M-936 & M-440. Which additional quantity was used based on obtained in process HCL salt weight.	NA

SPARSENTAN
Trail & Validation Status

SPARSENTAN

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Total No of Stages: 4
Stage Codes: SPAN1, SPAN2, SPAN3 & SPAN4 (API).
DMF stages: SPAN1, SPAN2, SPAN3 & SPAN4
No observations stages : Nil
Issues observed in below stages: SPAN1, SPAN2, SPAN3 & SPAN4

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
SPAN 1	SPAN100 125	Trail	During trial batch execution in Reaction-02 TLC Not complies (SPAN1 (i) content, Limit NMT 5.0%).	As per R&D Instructions extra 14gm of (M-1155) Tetrakis (triphenyl phosphine) (palladium (O) charged and maintained for 1hr then again checked the TLC but there is no further conversion then proceeded further operations.	SPAN1 (i) content Specification revised to 10% from 5%.
SPAN 1	SPAN100 125	Trail	Bromo ester impurity preparation-1 is 0.1475% preparation-2 is 0.1453% against the specification limit NMT 0.10% with reference OOS No.: **08-OOS24038**	Based on trial batch observation, R&D provided the Technical report to relaxation of in-process specification and Intermediate specification with reference technical report number R&D-13-TR-SRTN-240002-000 and R&D-13-TR-SRTN-240003-000 respectively	Based on Technical report and revised specification further manufactured the product.

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Total No of Stages: 4
Stage Codes: SPAN1, SPAN2, SPAN3 & SPAN4 (API).
DMF stages: SPAN1, SPAN2, SPAN3 & SPAN4
No observations stages : Nil
Issues observed in below stages: SPAN1, SPAN2, SPAN3 & SPAN4

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
SPAN 2	SPAN200 125	Trail	As per BPR maximum yield range is 79.19%, Obtained yield is 82.42%. (11.90 Kg yield obtained for 15.88 Kg input Batch Size)	This is the first scale-up batch in Plant, Yield may vary for proposed scale at plant level and it is proposed to revise the Yield in validation batches.	For validation batches yield range revised to (74.18% to 90.66%) from 64.89% to 79.19%).
			1). Op. No.61,64 & 148: As per BPR solvent to be distilled atmospherically at below 60°C, Distillate was not observed in plant scale at process temperature i.e. below 60°C. 2). Op. No. 215 & 218: Distilled under vacuum at below 45°C instead of atmospherically distillation at below 45°C	1) The reaction mass temperature is less than the boiling point of the solvent. (110.6°C for S-804 & 66°C for S-821). Hence distillation operation performed under vacuum at below 60°C. 2) Unreacted M-952 traces to be removed completely under vacuum distillation at below 45°C.	Proposed to distil the reaction mass under vacuum with respective temperature. V1, V2, V3 batches quality and yield results are within the limit.

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Total No of Stages: 4
Stage Codes: SPAN1, SPAN2, SPAN3 & SPAN4 (API).
DMF stages: SPAN1, SPAN2, SPAN3 & SPAN4
No observations stages : Nil
Issues observed in below stages: SPAN1, SPAN2, SPAN3 & SPAN4

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
SPAN 3	SPAN300 125	Trail	As per BPR compound should be dissolved completely in S-806 during Stirring the reaction mass for 20 to 30 min. at 60°C ± 5°C. Hazy mass observed after 20-30 min maintenance at 60±5°C.	Complete dissolution is required to get desired yield and quality, hence temperature raising is required till complete dissolution.	Reaction mass temperature increased to 68.0°C for complete dissolution.
SPAN 4	SPAN400 125	NA	In-process sample (Sample No. SPAN4-02) HPLC analysis of Any individual unspecified impurity obtained results is 0.09% against the specification limit NMT 0.08% without purification.	The batch were taken for further purification as per approved batch production record.	Based on pre-validation batch IPC results, default purification recommended without in-process HPLC testing.

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Total No of Stages: 4
Stage Codes: SPAN1, SPAN2, SPAN3 & SPAN4 (API).
DMF stages: SPAN1, SPAN2, SPAN3 & SPAN4
No observations stages : Nil
Issues observed in below stages: SPAN1, SPAN2, SPAN3 & SPAN4

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
SPAN4	SPAN400325 SPAN400425	NA	Single Purification is available in BPR. As per In-house spec MSI impurity limit is 0.1% (obtained result was ~0.08-0.09)	To meet customer (Teva) requirement (MSI NMT 0.06) extra purification was performed for Validation-02 & Validation-03 batches.	

MARIBAVIR
Trail & Validation Status

MARIBAVIR

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Total No of Stages: 6
Stage Codes: MBIR1, MBIR2, MAVR1, MRBR1, MRBR2 & MRBR3 (API).
DMF stages: MRBR1, MRBR2 & MRBR3.
No observations stages : NA
Issues observed in below stages: MBIR2 & MAVR1

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
MBIR2	MBIR200124	Pre-validation	During trial batch execution Sample No. MBIR2-01 not meeting the specification w.r.t. MBIR1 content by HPLC Obtained result is 2.4%, Limit NMT 1.0%.	This is first scale up batch in plant, reaction conversion is slow in proposed facility with proposed batch size. Based on R&D suggestion the batch was proceed to next operation with obtained results (2.4%) after 49 hrs. maintenance.	Based on purging study data, and Addendum-1 to PDR received from R&D with reference PDR No: PDR/MBVR/2023/00, MBIR1 content limit revised from NMT 1.0%w/w to NMT 4.0%w/w for validation batches. V1, V2 & V3 batches quality & Yield results are within the specification limit.
MAVR1	MAVR100124	Pre-validation	During trial batch execution AIUI was observed (1.0748% & 2.1460%) with Ref. Out of Specification No.: OOS No: 08-OOS25001.	As per R&D instruction, Impurity (RTT~0.21) was not observed in the earlier batches and the impact of longer hours holding of the batch material is uncertain. However, the re-process procedure can be adopted to getting the desired quality of MAVR1 (Reference Development Report No.: PDR/MBVA/2023/00).	Based on the R&D recommendation, other pending analyses has been terminated, and the batch was rejected. The Rejected batch was re-processed under batch number MAVR100125RP and quality results are complies, Same re-process procedure was included in validation batches. V1, V2 & V3 batches quality & Yield results within the specification limit.

MARIBAVIR

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Total No of Stages: 6
Stage Codes: MBIR1, MBIR2, MAVR1, MRBR1, MRBR2 & MRBR3 (API).
DMF stages: MRBR1, MRBR2 & MRBR3. .
No observations stages : NA
Issues observed in below stages: MAVR1

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
MAVR1	MAVR100124	Pre-validation	it was observed that the required equipment number (I/GLR/36) was not included in the BPR Format No. F-MAVR1-01/00, for the distillation activity with Reference Deviation No: 08-DR-24-044.	Based on deviation, the reactor I/GLR/36 was used for further distillation operation and cleaned.	The reactor included in validation batches.

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Total No of Stages: 6
Stage Codes: MBIR1, MBIR2, MAVR1, MRBR1, MRBR2 & MRBR3 (API).
DMF stages: MRBR1, MRBR2 & MRBR3. .
No observations stages : NA
Issues observed in below stages: MRBR1 & MRBR2

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
MRBR1	MRBR100125	Pre-validation	During complete analysis Assay by HPLC 90.1783% w/w observed (Limit: NLT 97% & NMT 102%w/w) During RS by HPLC Alpha anomer impurity is 5.8470% (Limit: NMT 0.5%) and Total impurities are 6.1160% (Limit: NMT 3.0%) with reference OOS No.: 08-OOS25003 & 08-OOS25003 respectively.	Based on investigation batch was rejected and taken for Re-process under batch Number MRBR100125RP, the reprocess batch quality results are complies. same re-process procedure was included in validation batches	Based on R&D suggestion the manufacturing process to be validated to in line with addendum-5 to product development report number PDR/MBVR/2023/00. (IPA(S-806) Qty increased, crude drying introduced, temp changed, Yield range changed) V1, V2 & V3 batches quality & Yield within the specification limit.
MRBR2	MRBR200125	Pre-validation	1) The raw material M-3149 should charge quantity is 10 volumes, bat in pre-validation batch M-3149 material charged as 11 volumes	1) M-3149 (Isopropyl Amine) is low boiling (32.4°C) and high volatile liquid, hence evaporation loss will be more in plant scale batch during solution preparation, reaction mass maintenance and at reflex some of the M-	M-3149 quantity 11 volumes used in validation batches.

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Total No of Stages: 6
Stage Codes: MBIR1, MBIR2, MAVR1, MRBR1, MRBR2 & MRBR3 (API).
DMF stages: MRBR1, MRBR2 & MRBR3.
No observations stages : NA
Issues observed in below stages: MRBR2 & MRBR3

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
MRBR2	MRBR200225	V1 Deviation	During Validation (MRBR200225)(V1) batch execution Lower yield was observed i.e.; 2.40Kg for 12.30 Kg input batch size (Yield range is 2.55Kg to 3.83Kg) with reference Deviation No.: 08-DR-25-016.	Investigation performed against the lower yield and concluded, and further two validation batches (V2) & (V3) monitored and yield are with in the range.	NA
MRBR2	**MRBR200325 MRBR300425**	**V2 & V3**	**During Validation-02 & Validation-03 execution**	**Extra purification was performed in Validation-02 & Validation-03 due to MSI ~0.1 observed at 1.89 RRT (Limit: NMT 0.1), after Purification-04 MSI reduces to ~0.07**	**NA**
MRBR3	MRBR300125	Pre-validation	As per BPR, Material to be dried for 8 to 10 hours under vacuum at 65±5°C. Methanol Solvent content by GC results after 9th hour 2412ppm and after 10th hour 2315ppm against the	Small lumps formation observed in reactor during crystallization & in PNF during filtration. Methanol solvent might be trapped in lumps that may lead to failure of methanol content in GC analysis, after 9th hour and	As per R&D instruction, the batch was proceeded for milling operation followed by drying for 4 to 6 hours under vacuum at 65±5°C,and samples are submitted and

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Total No of Stages: 6
Stage Codes: MBIR1, MBIR2, MAVR1, MRBR1, MRBR2 & MRBR3 (API).
DMF stages: MRBR1, MRBR2 & MRBR3.
No observations stages : NA
Issues observed in below stages: MRBR3

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
MRBR3	MRBR300225	V1 Deviation	As per BPR sample submitted for GC for 5th hour and 6th hour Methanol Solvent content by GC results are 3607ppm & 3168ppm against the specification limit of 3000 ppm with Deviation No.: 08-DR-25-018	Based on deviation, the batch material was dried up to 16 hour through Annexure to the existing BPR and RS by GC results are within the specification limit. Based on V1 batch IPC results, BPR has been revised with fixing the drying time and addendum to protocol prepared to execute the further two more validation batches.	Same drying operation was included in master BPR and executed for V2 & V3 batches
	MRBR300225	V1 Deviation	It was observed that the Methanol content obtained in the Residual Solvents by GC test for the first validation batch (B. No.: MBR0020325) is inconsistent when compared to the results of the second and third validation batches (Ref. Deviation No.: 08-DR-25-019)	Based on deviation investigation conclusion, the residual solvent by GC re-analysis results are considered for reporting for first validation batch of Maribavir Stage MRBR3.	NA

CARBIDOPA
Trail & Validation Status

CARBIDOPA

Total No of Stages: 3
Stage Codes: CRDP1, CRDP2 & CRDP3 (API).
DMF stages: CRDP1, CRDP2 & CRDP3.
No observations stages : NA
Issues observed in below stages: CRDP1.

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Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
CRDP1	CRDP100125	Trial	1). Material was not isolated in below 7.0 pH. 2) During trial batch execution Low Yield obtained, 20.50 Kg against the standard yield Range 24.10Kg to 29.45Kg for 35 Kg input batch Size.	Material isolation observed at above 7 pH (7.03) as per BPR pH range is (6.5-7.5), Based on Addendum-1 to PDR, Process modified by changing pH adjustment parameter from 6.5-7.5 to 7.3-8.0 for validation batches).	it concluded that during the solid isolation pH playing a Vital role for yield, so the lower side pH is causing lower side yieldand. addendum-1 to PDR (Ref. PDR No.: PDR/CBDP/2023/00 Based on recommended process Three validation batches (V,. V2, V3) were executed and quality & Yield results are within the specification limit.

CARBIDOPA

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Total No of Stages: 3
Stage Codes: CRDP1, CRDP2 & CRDP3 (API).
DMF stages: CRDP1, CRDP2 & CRDP3.
No observations stages : NA
Issues observed in below stages: CRDP2

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
CRDP2	CRDP20012 5	Pre-validation	During the Pressure Nutsche filter operation , Toluene ML's,/ Toluene traces in the material was not reduced even after prolonged suck dry in the Pressure Nutsche Filter.	Initially Pressure Nutsche filter is used for the ML's filtration followed by centrifuge also used for the Spin drying the material for complete removal of Toluene traces from the material.	Filtration operation recommended PNF followed by Centrifugation. Three Validations batches manufactured and quality and yield results are within the specification limit.
CRDP3	CRDP30012 5	Pre-validation	Op.No.13 & 14: reaction mass temperature has to be raised at 80± 5°C, but is observed that the reaction mass temperature was not raising beyond 74.8°C.	The process solvent is Ethyl Acetate boiling point is 77°C , in the presence of material the solvent started to reflux temperature at 74.8 °C, due to solvent reflux temperature was not increased beyond 74.8°C.	Based on R&D instruction, validation BPR has been prepared with the temperature 75±5°C instead of 80±5°C. Three validations completed and quality & Yield results are within the specification limit.

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LISINOPRIL DIHYDRATE
Trail & Validation Status

LISINOPRIL DIHYDRATE

MSN Life Sciences Private Limited

Total No of Stages: 2
Stage Codes: LDPH1 & LDPH2 (API).
DMF stages: LDPH1 & LDPH2
No observations stages : NA
Issues observed in below stages: LDPH1 & LDPH2.

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
LDPH 1	LDPH100 125	Pre-validation	Impurity F & AIUI failed w.r.t 0.87% (NMT 0.30%) & 1.69% (NMT 0.5%)	Trial Batch was purified in Aq. Ethanol based on Addendum-1 to Developed Report No PDR/LSPR/2024/00, batch quality results are within the specification limit. Re-process taken and same was included in validation.	V1, V2, & V3 batches manufactured with Aq. Ethanol process , and all three validation batches quality and yield results are within the specification limit.
LDPH 2	NA	Validation	**In the Batch LPDH200225 Nitrosamines obtained were 67 ppm against NMT 17.5 PPM.** **Output obtained : 94.0 kg and RS by HPLC was well within the pre-determined**	**This batch was taken for the ethanol slurry (as per R&D Process) in the I-Block phase-IV in two equal lots with Lot size of 46.0 Kg each, After the Ethanol slurry Nitrosoamines were reduced to required level and met the specification, XRD of the material has no changes and matched with the regular material, The overall yield obtained was**	**All the validation batches purification done and well within the limits.**

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Trail & Validation Status

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Total No of Stages: 3
Stage Codes: CNBD1, CNBD2 & CNBD3 (API).
DMF stages: CNBD1, CNBD2 & CNBD3
No observations stages : CNBD1
Issues observed in below stages: CNBD2 & CNBD3.

Stage No.	Batch Number	Activity	Description of the Issue	Action Proposed	Remarks
CNBD2	CNBD200124	Trial	CNBD200124 obtained final product yield (5.15Kg & 48.80%) is higher side of the Trial batch yield range of (30.80 % to 46.20%).	Revised the Yield Range with ±10% of the Trial batch obtained yield for Validation.	All three validation are within the limit.
CNBD3	CNBD300124	Trial	During the execution of trial batch, the In-process sample (Sample No. CNBD3-03) HPLC analysis of Any individual unspecified impurity obtained results is near to the specification limit, the obtained results is 0.05% w/w against the specification limit NMT 0.05%w/w. The trial batch obtained yield is higher side of the specification limit.	Based on R&D instruction, the material were taken for optional purification as per approved batch production record. Based on the obtained results the yield is recommended for ±10% of the obtained trial batch yield.	Based on the trial batch recommendation purification performed the all thee validation batches. V1, V2 & V3 quality and yield results within the specification limit.